



Sheppard Pratt
HEALTH SYSTEM

KKOLMAC
Outpatient Recovery Centers
Leaders in addiction treatment since 1973

Pharmacological Management Of Opioid Use Disorders

George Kolodner, M.D.

Chief Clinical Officer, Kolmac Outpatient Recovery Centers
Clinical Professor of Psychiatry,
Georgetown and University of Maryland Schools of Medicine

Sunil Khushalani, M.D.

Medical Director, Adult Service Line, Sheppard Pratt Health System
Clinical Assistant Professor of Psychiatry,
University of Maryland School of Medicine

SUBSTANCE USE DISORDERS

○ Substance use disorders are most effectively treated when approached as a **chronic disease**, similar to diabetes

○ Can be **managed** but not **cured**

○ Treatment goal is **"recovery"**



FRAME OF REFERENCE: CHRONIC DISEASE

- **Addiction:** continued use despite adverse consequences
- **Physical dependence:** signs and symptoms experienced upon the abrupt discontinuation of a substance (withdrawal)
- “Dependence” eliminated from **DSM-5**

ADDICTION Vs. PHYSICAL DEPENDENCE

OUTLINE

○ Historical Background

○ Current context

○ Psychopharmacology

OUTLINE

HISTORICAL BACKGROUND

3400 BC



First record of opium cultivation

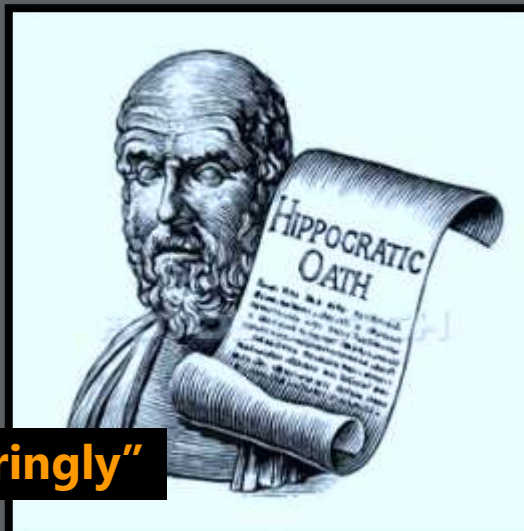
1853



"Decrease addiction by avoiding stomach"

Morphine isolated from opium

"Use Sparingly"



400 BC



1806



1898

1996



Aggressive marketing of ER formulations

1999



VA and JCAHO to treat pain as the "5th vital sign"

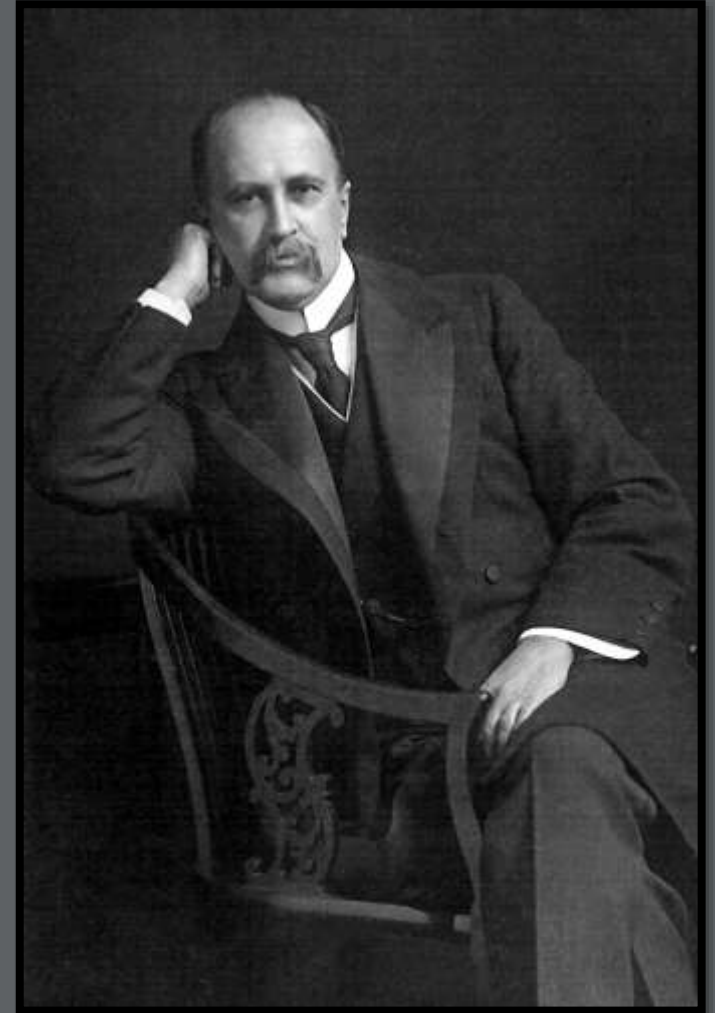
Safety Reassurances by pain management specialists and manufacturers

- **1870s – 80s:** Overuse of hypodermic injection by physicians
- **1890's – 1910s:** Change to more balanced prescribing patterns through education and pressure by reform-minded physicians and pharmacists

NEJM. David Courtwright, Preventing and Treating Narcotic Addiction

19TH C. OPIOID MEDICATION EPIDEMIC

“Man has an inborn **craving for medication**. Heroic dosing for several generations has given his tissues a thirst for drugs... It is really one of the **most serious difficulties** with which we have to contend. Even in minor ailments, which would yield to dieting or to simple home remedies, the doctor’s visit is **not thought to be complete** without the prescription”



DR. WILLIAM OSLER'S OPINIONS

- 1914: Harrison Narcotic Act was **intended** to keep narcotic transactions within legitimate medical channels
 - Actually implemented by Treasury Department in a way that **interfered** with treatment of addiction

CRIMINALIZATION OF OPIOID ADDICTION AND TREATMENT

○ 1919: Supreme court supported enforcement

○ The treatment of opioid addiction is “outside the realm of legitimate medical interest”

-Webb et al vs. United States



CRIMINALIZATION OF OPIOID ADDICTION AND TREATMENT

- Controlled Substances Act (1970) is successor to Harrison Act
 - Enforced by Drug Enforcement Administration (DEA) which has ultimate authority (versus FDA) for determining medication schedule (I to IV)

CRIMINALIZATION OF OPIOID ADDICTION AND TREATMENT

CURRENT CONTEXT

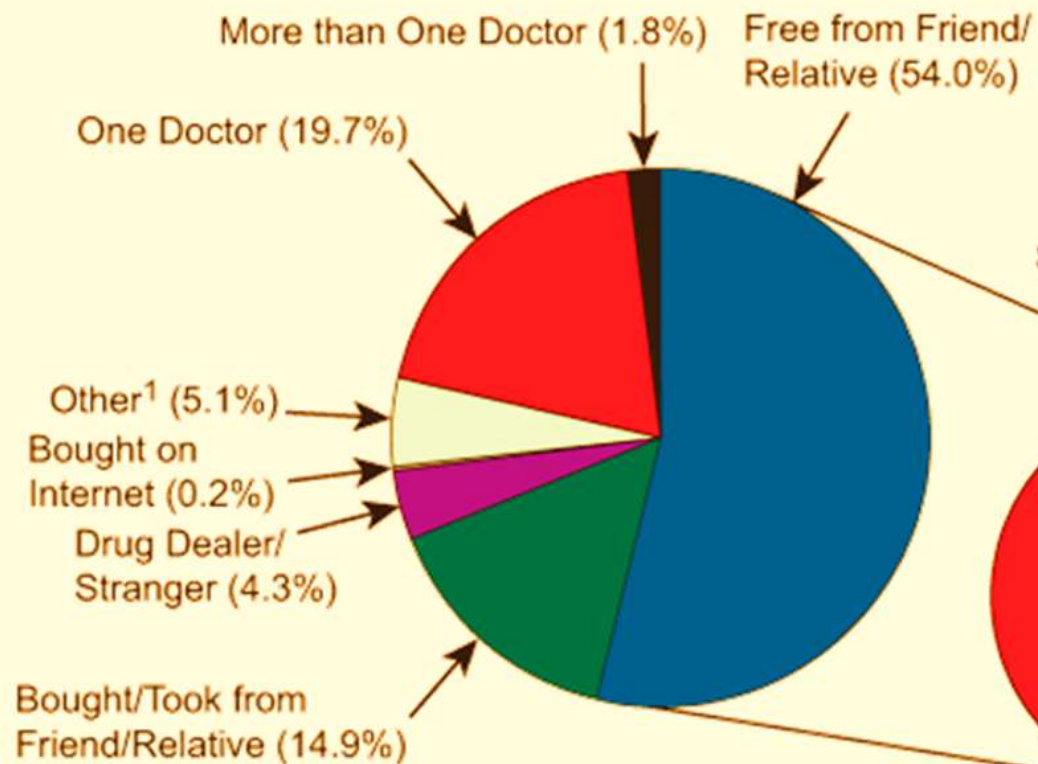
- **Wave 1:** Overprescribing of opioids
 - Established market for opioid use outside of inner cities
- **Wave 2:** Heroin
 - Shift due to cost from increased tolerance
- **Wave 3:** Fentanyl
 - Added to heroin to increase potency

CURRENT OPIOID EPIDEMIC: 3 WAVES

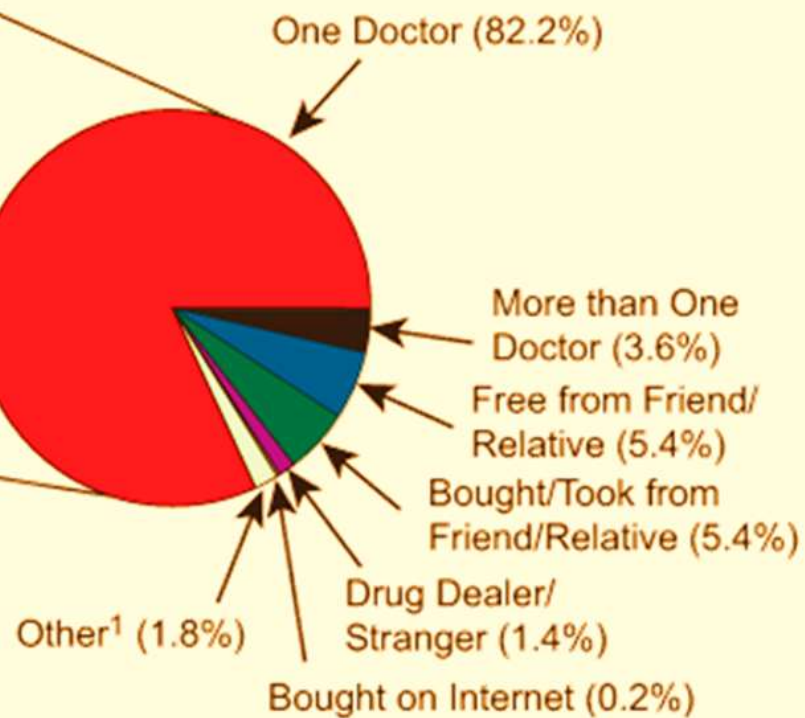
- **1990s to present:** Overprescribing of opioids
 - Increased attention to pain management- well intentioned
 - Not accompanied by education of physicians
 - Exploited by pharmaceutical companies
 - Purdue Pharmaceuticals, OxyContin

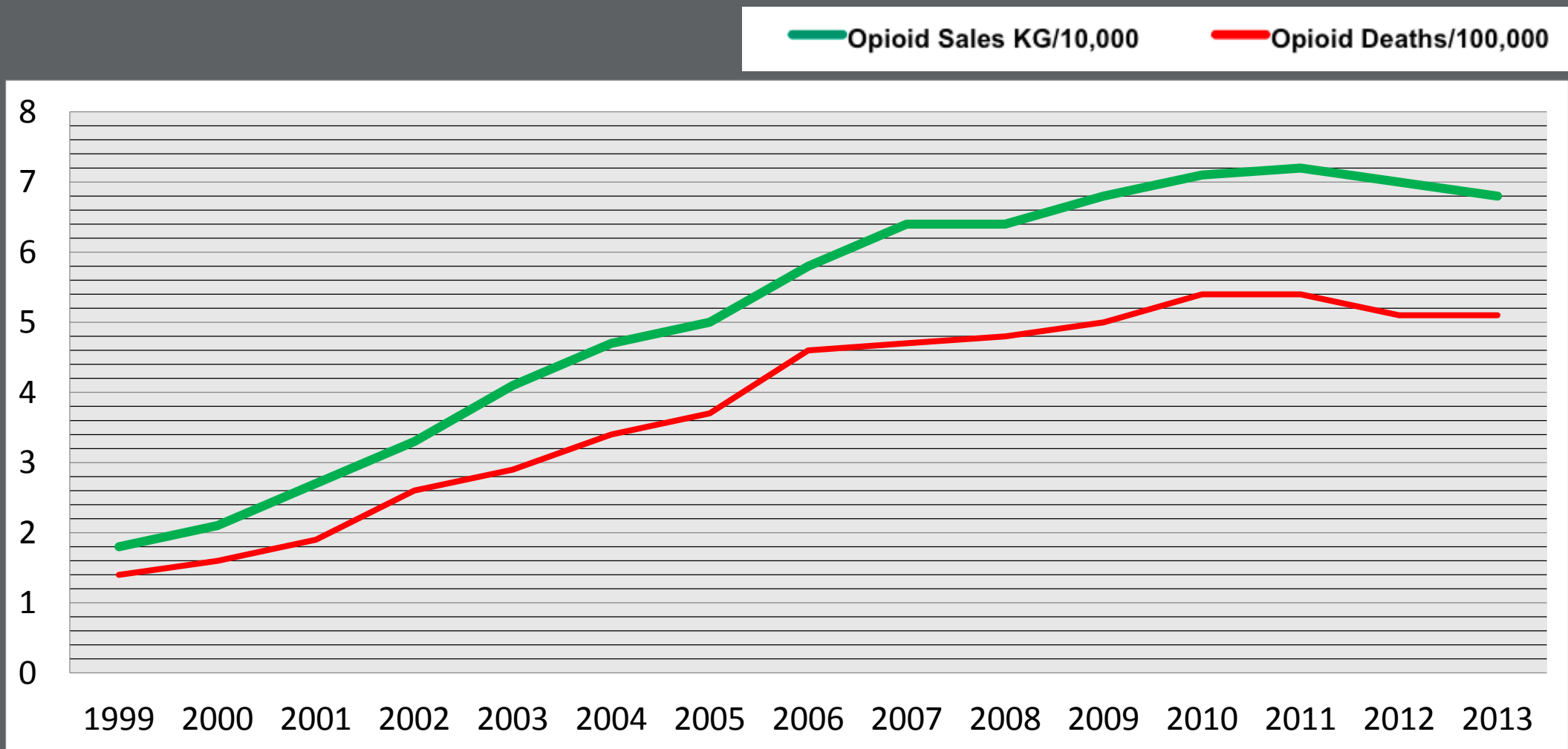
CURRENT OPIOID EPIDEMIC: 1990 to PRESENT

Source Where User Obtained



Source Where Friend/Relative Obtained

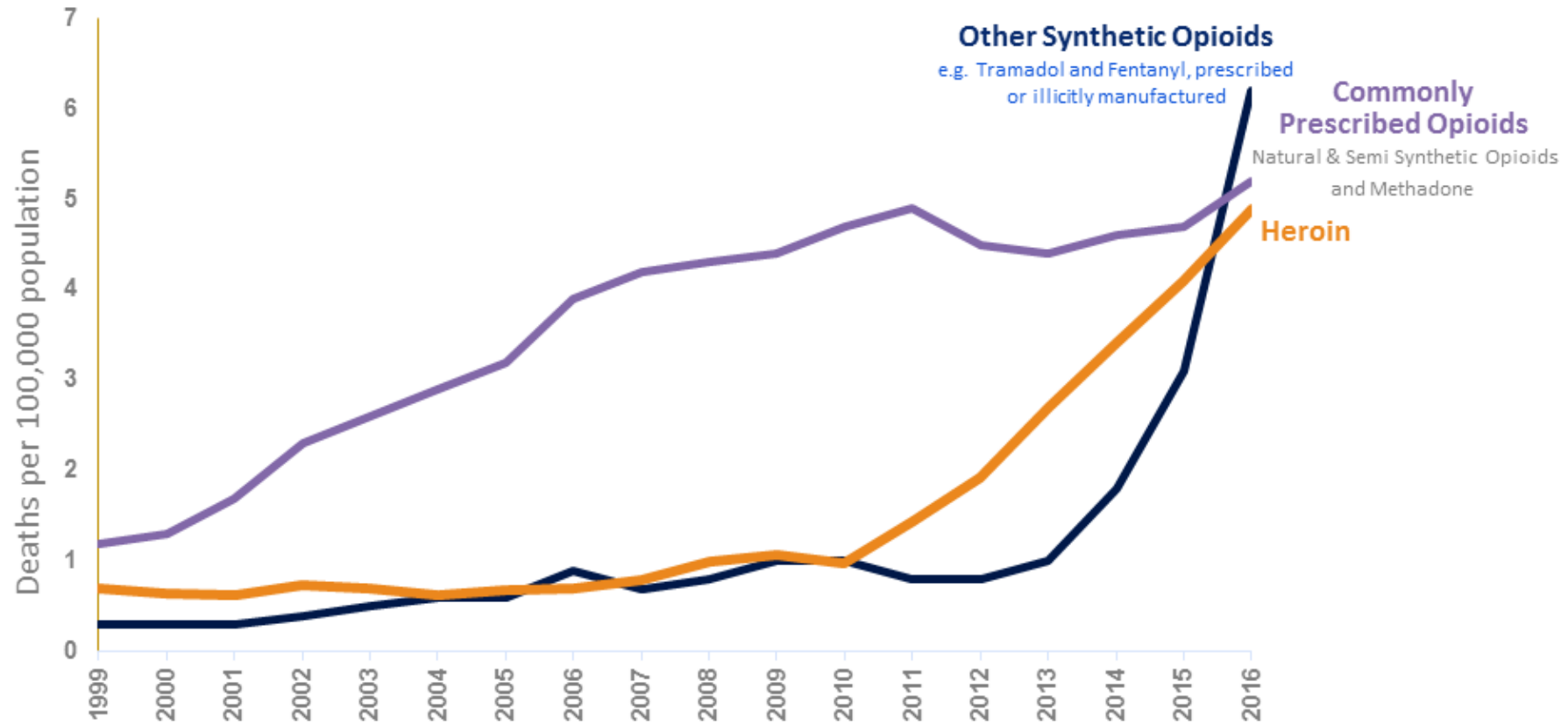




Source: National Vital Statistics System, DEA's Automation of Reports and Consolidated Orders System

CURRENT OPIOID EPIDEMIC: 1999-2013

3 Waves of the Rise in Opioid Overdose Deaths



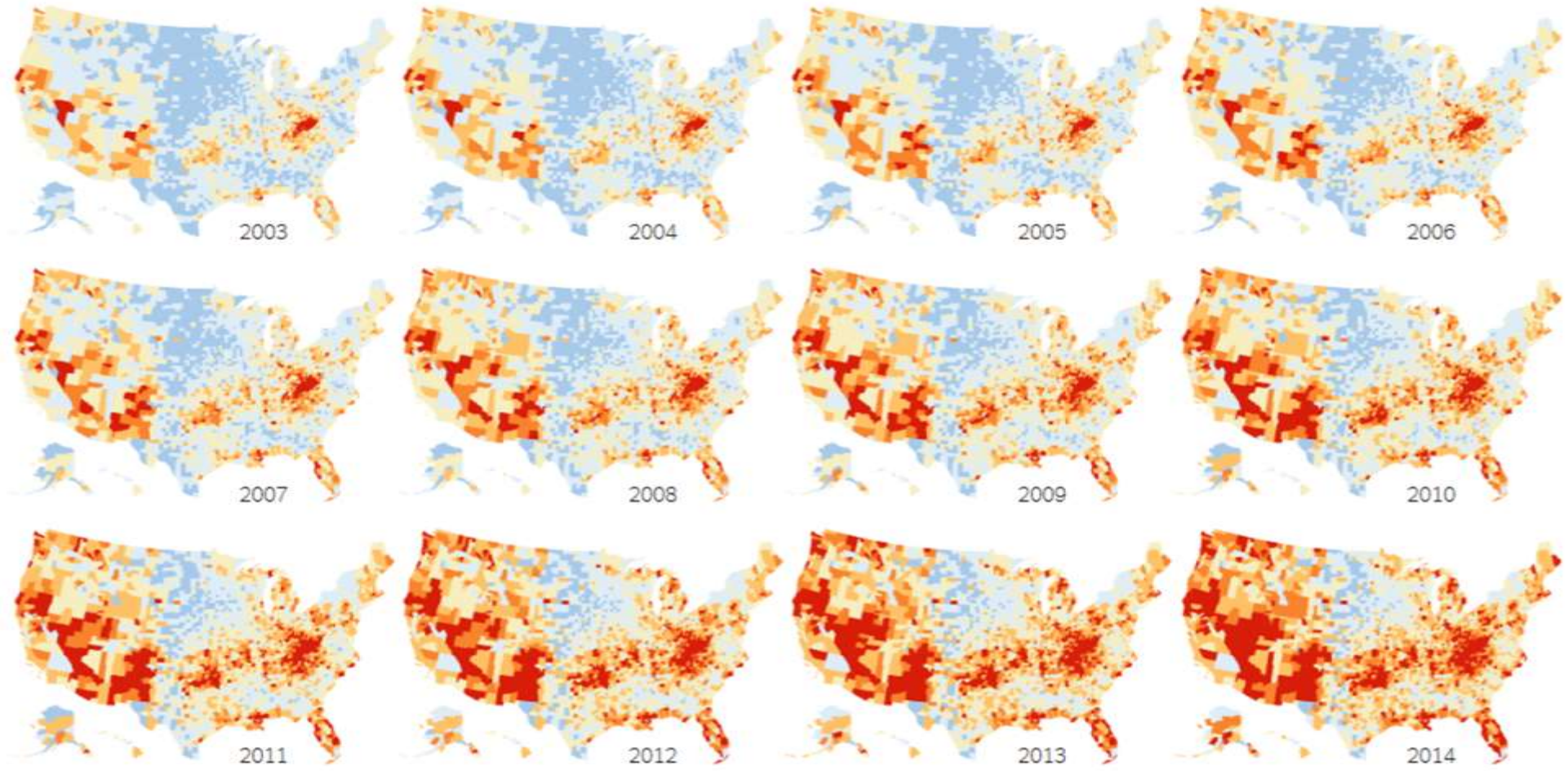
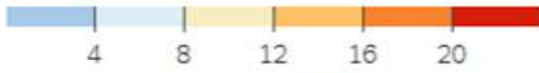
Wave 1: Rise in Prescription Opioid Overdose Deaths

Wave 2: Rise in Heroin Overdose Deaths

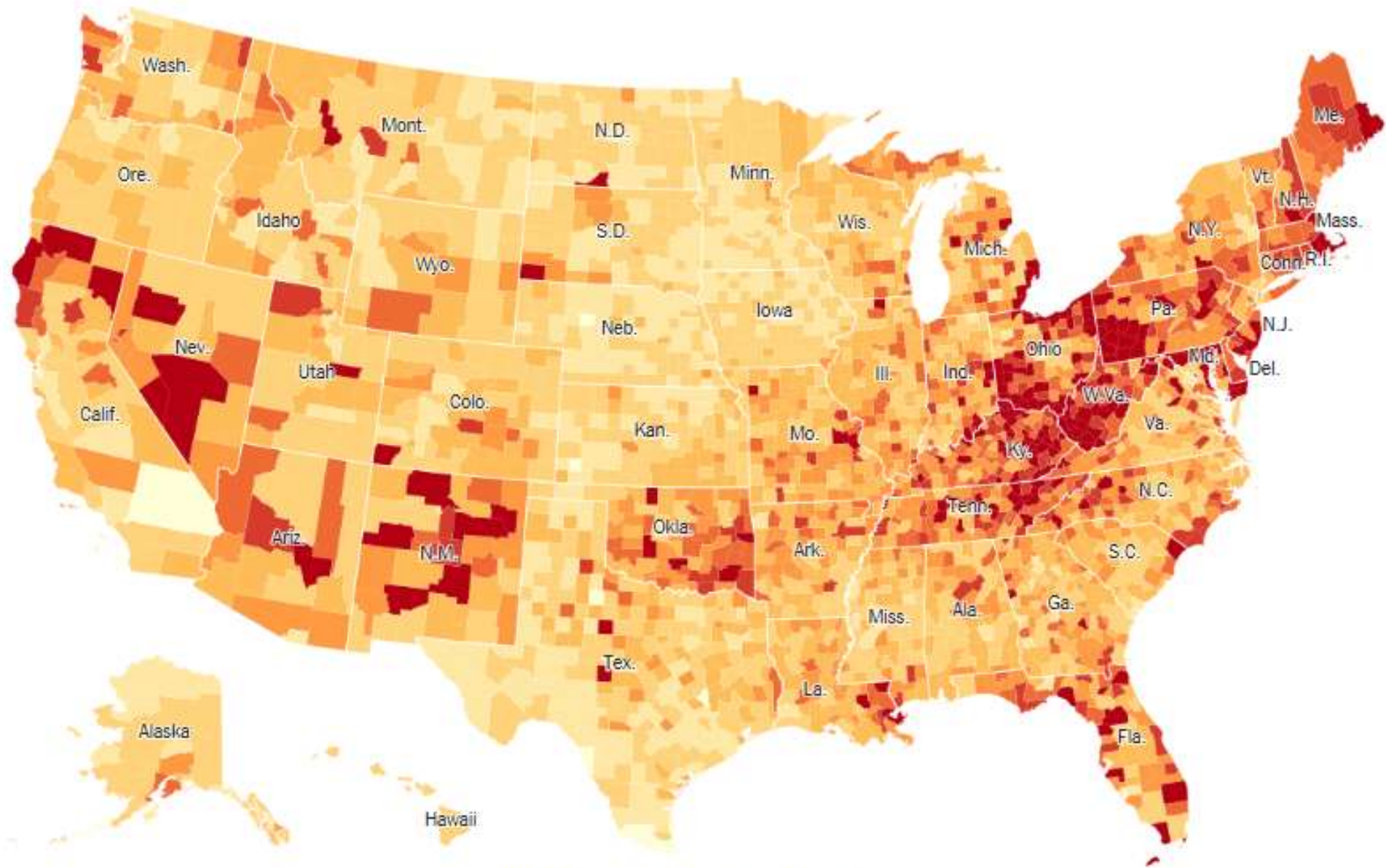
Wave 3: Rise in Synthetic Opioid Overdose Deaths

SOURCE: National Vital Statistics System Mortality File.

Overdose deaths per 100,000



Deaths from drug overdoses have jumped in nearly every county across the United States, driven largely by an explosion in addiction to prescription painkillers and heroin.



2016 drug overdose deaths per 100,000 residents

5 10 15 20 25 30 35

PSYCHOPHARMACOLOGY

- **Full agonist:** attaches to opioid receptor and **fully** activates it
 - Opium, morphine, codeine, oxycodone (OxyContin, Percocet), hydrocodone (Vicodin), methadone

SOME BASIC TERMS

○ **Antagonist:** attaches to opioid receptor and **blocks it** instead of activating it

○ Naltrexone (Revia, Vivitrol)

SOME BASIC TERMS

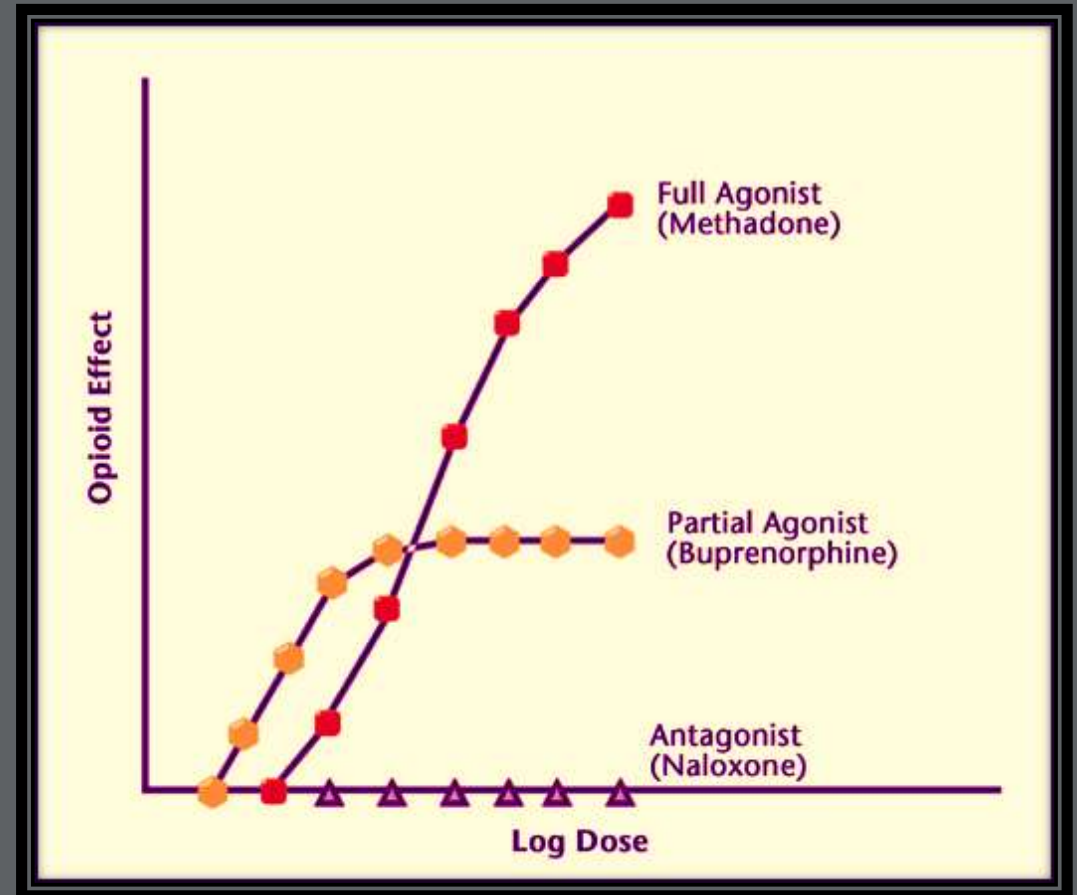
- **Partial agonist:** attaches to opioid receptor, **partially** activates and blocks it
 - Buprenorphine (Suboxone, Subutex)

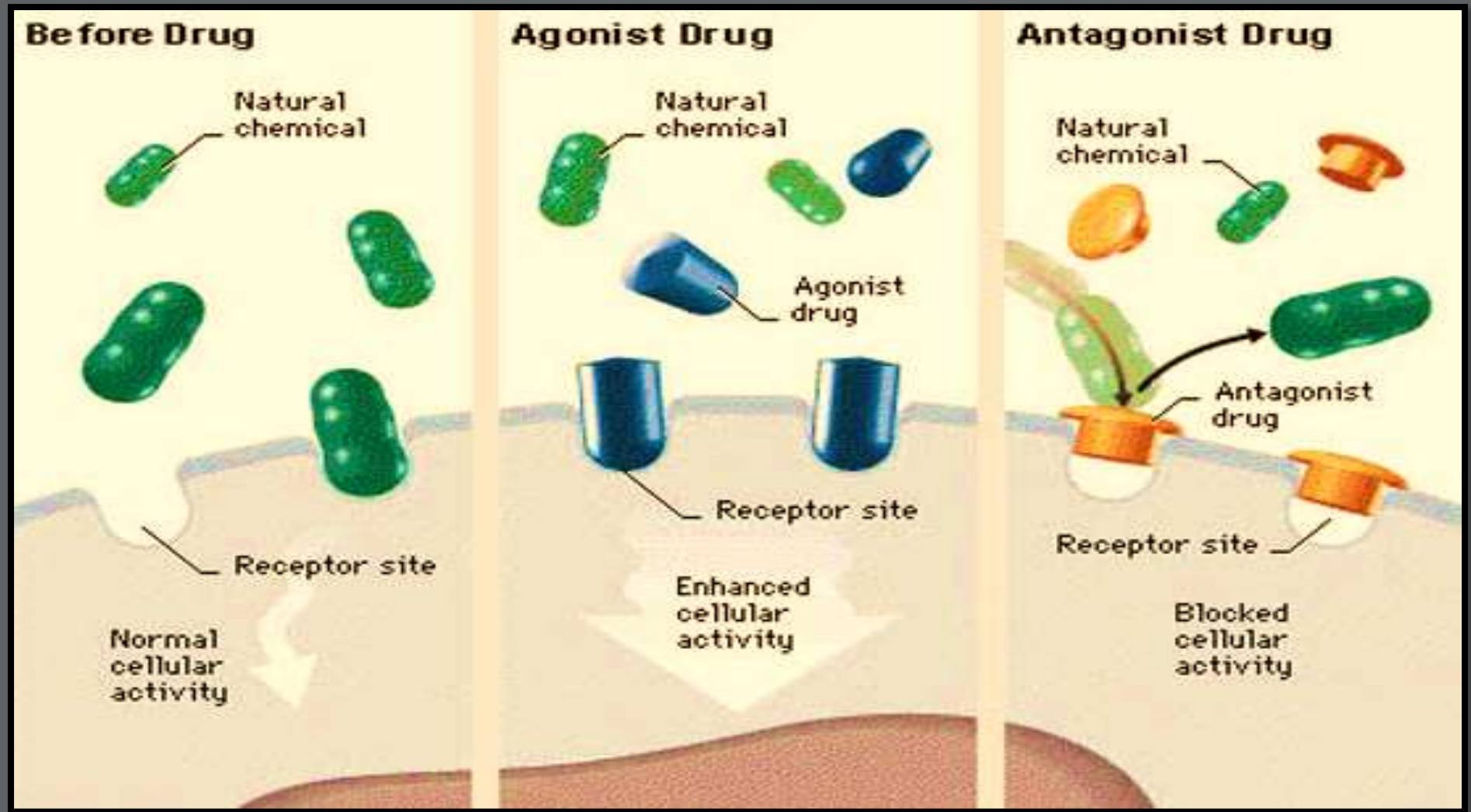
SOME BASIC TERMS



Affinity for receptor determines which agent is displaced from receptor

SOME BASIC TERMS





SOME BASIC TERMS

○ Blocking effect

- If antagonist is attached to the receptor site, agonist will have no effect

○ Precipitated withdrawal

- If agonist is attached to receptor site, antagonist will displace it and trigger the abrupt onset of severe withdrawal symptoms

IMPORTANCE OF SEQUENCE

- Compared to alcohol use disorders: **greater reliance** on relapse prevention medications for better outcomes
- High relapse rates **when medications are discontinued**
 - 5 year standard for recovery does not hold

HOW LONG TO STAY ON MEDICATIONS?

1914



The Harrison Narcotics Act of 1914 was a United States federal law, which regulated and taxed the production and distribution of opiates and coca products.

Criminalized opioid dependency

1964

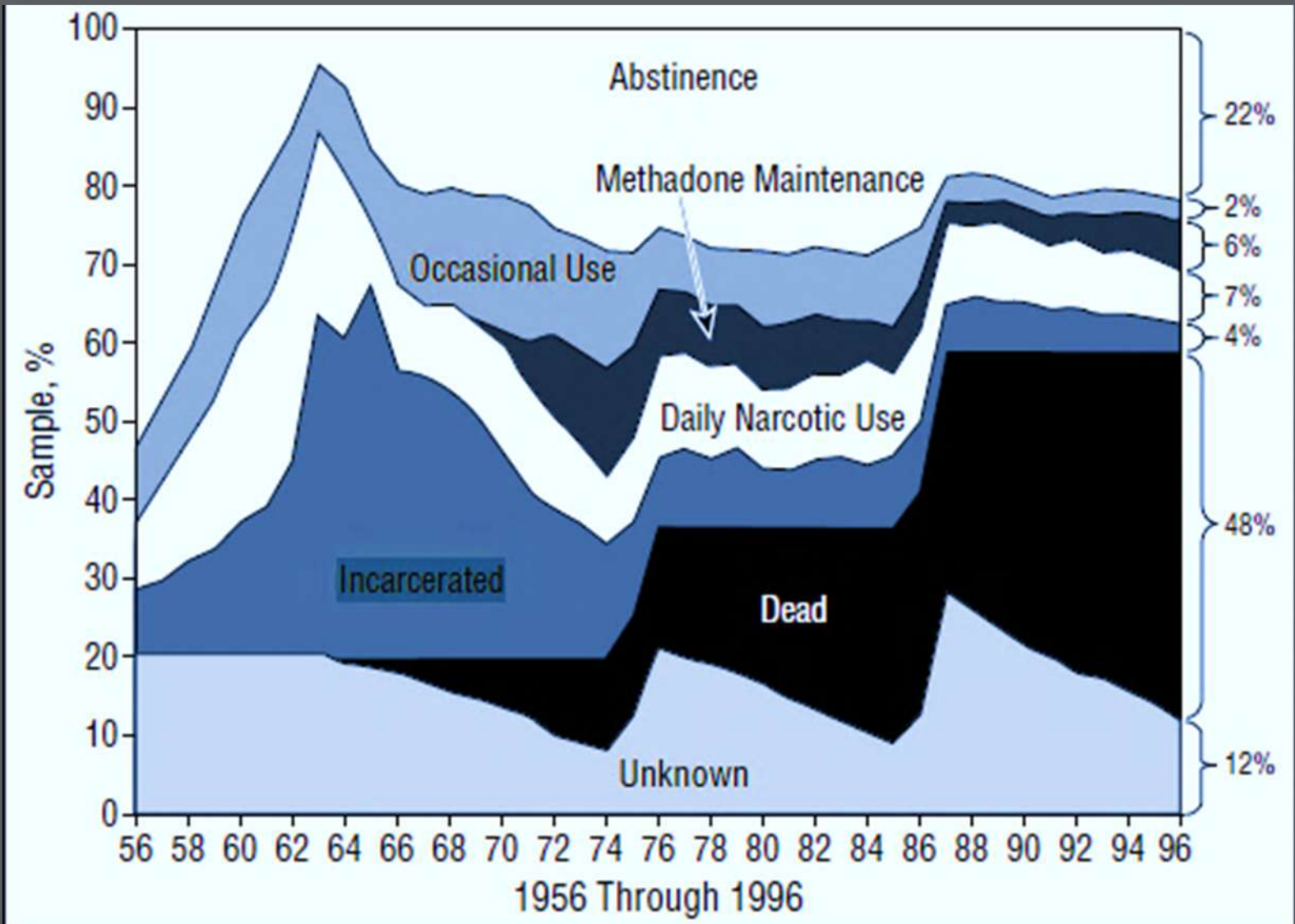


Methadone maintenance

2000



**DATA 2000 Waiver
Enabled physicians to prescribe buprenorphine**



The natural history of narcotics addiction among a male sample (N=581) over a 33 year period

Without maintenance pharmacotherapeutic agents the prognosis is quite poor

○ Non-agonist medication

- Withdrawal management: non-specific supportive medication
- Ongoing recovery support: opioid antagonist

TWO STRATEGIES

○ Agonist medication

- Withdrawal management: full or partial opioid agonist
- Ongoing recovery support: opioid agonist

TWO STRATEGIES

○ Alpha-2 adrenergic agonists are the cornerstone

○ Reduce adrenergic hyperactivity in upregulated locus coeruleus

○ Agents

Clonidine most common

Guanfacine has less hypotension and sedation

Lofexidine is newest addition

NON-AGONIST WITHDRAWAL MANAGEMENT

○ Supportive medications for other symptoms

○ **Anxiety**: phenobarbital

○ **Insomnia**: sedating antidepressants, quetiapine

○ **Nausea**: ondansetron

NON-AGONIST WITHDRAWAL MANAGEMENT

- Naloxone (Narcan)
- Short acting antagonist
- Two formulations
 - Parenteral
 - Nasal Spray

**YOU CAN
STOP
OVERDOSE
DEATH**

GET NALOXONE SAVE A LIFE

NALOXONE: (also called Narcan[®]) is a prescription medicine that can stop an overdose. Parents, relatives and friends can get it and give it to someone who is overdosing on heroin or other drugs like OxyContin[®] or Percocet[®].

WHAT IS **NALOXONE** ?

Naloxone is a prescription medicine that can reverse an **opioid** overdose. It can be administered by nasal spray or injection.

OVERDOSE REVERSAL: OPIOID ANTAGONIST

○ Issues

- Larger doses required to reverse “fentalogues”
- Lack of follow up treatment

OVERDOSE REVERSAL: OPIOID ANTAGONIST

○ Oral (Revia)

- 24 hour effective duration

- Extend to 72 hours by giving 150 mg

○ Depot parenteral lasts 30 days (Vivitrol)

- Large volume requires gluteal intramuscular injection

NALTREXONE FORMULATIONS

- Must allow opioid **washout period of several days** before beginning oral
 - Length of washout depends on opioid being used
 - Some protocols use early administration of .5 mg to 1 mg doses prepared by compounding pharmacist
- **Precede** parenteral with one week of oral

NALTREXONE INITIATION

- No psychoactive effect
 - Blocks psychoactive effect of opioid agonists
- Philosophical preference by some patients and corrections officials

NALTREXONE BENEFITS

- **Black box warning** for oral formulation for hepatic toxicity
 - **Extremely rare** at 50 mg dose
- **Short term:** initiation more difficult than with agonists

NALTREXONE ISSUES

- Long term: poor adherence

- Side effects:

 - Need to over-ride if emergency requires opioid analgesia

 - Oral: nausea

 - Parenteral: site injection pain

NALTREXONE ISSUES

- **1964:** First used by Dole and Nyswander
 - Harassed until formal approval in 1971
- Dispensed, **not prescribed**, in highly regulated settings
 - **Can** be prescribed for pain
- **Better long-term outcomes** than abstinence programs

METHADONE



- Based on opioid's relation to **stress response system**
- Addictive use of opioids creates **persistent disruption** of hypothalamic-pituitary-adrenal axis
 - **Abstinence:** hyper-responsive
 - **Heroin:** hypo-responsive
 - **Methadone:** normal response

METHADONE THEORY

- Use low initial dose and **increase slowly** to prevent overdose by long acting metabolites
- Use **high enough maintenance dose** to block euphoric effect of other opioids
 - Usually 60 mg or higher
- **Taper off slowly** over several months (usually blind)

METHADONE KEYS

Methadone Maintenance 4 Decades Later Thousands of Lives Saved But Still Controversial

SUMMARY OF THE ORIGINAL ARTICLE

A Medical Treatment for Diacetylmorphine (Heroin)
Addiction: A Clinical Trial
With Methadone Hydrochloride

Vincent P. Dole, MD, and Marie Nyswander, MD

JAMA. 1965;193(8):646-650.

Twenty-two male patients, addicted to heroin 9.5 years (median), were stabilized using oral methadone hydrochloride and then observed for approximately 1 to 15 months (median, 3 months). The medication had 2 main effects: (1) relief of narcotic hunger (craving); and (2) induction of sufficient tolerance to block the average illegal dose of heroin.

A combination of the methadone treatment and a comprehensive program of rehabilitation was associated with marked improvement in patient problems such as jobs, returning to school, and family reconciliation. No adverse effect other than constipation was found.

The authors note that "careful medical supervision and many social services" were necessary and stressed that "both the medication and supporting program were essential." The small size of the group studied and short duration of the follow-up would best describe this as a promising and exciting but preliminary report.

See www.jama.com for full text of the original *JAMA* article.

Commentary by Herbert D. Kleber, MD

Heroin became the street narcotic of choice. During World War II, with heroin scarce and purity as low as 1%, addic-

METHADONE CONTROVERSIES



METHADONE CONTROVERSIES

- Originally **intended as supportive medication** for comprehensive treatment program
 - Psychosocial components **reduced over time**
- **Stigmatized** over time

METHADONE CONTROVERSIES



In 1990, the Office of National Drug Control Policy stated clearly that methadone maintenance was both **legitimate and an important part** of the spectrum of drug abuse treatment



**WHO Model List
of
Essential Medicines**

18th list
(April 2013)
(Final Amendments – October 2013)

24.5 Medicines for disorders due to psychoactive substance use	
nicotine replacement therapy (NRT)	<p>Chewing gum: 2 mg; 4 mg (as polacrilex).</p> <p>Transdermal patch: 5 mg to 30 mg/16 hrs; 7 mg to 21 mg/24 hrs.</p>
<i>Complementary List</i>	
<input type="checkbox"/> <i>methadone*</i>	<p><i>Concentrate for oral liquid: 5 mg/ml; 10 mg/ml (hydrochloride).</i></p> <p><i>Oral liquid: 5 mg/5 ml; 10 mg/5 ml (hydrochloride).</i></p> <p><i>* The square box is added to include buprenorphine. The medicines should only be used within an established support programme.</i></p>

- In October 2002, FDA approved **two** Schedule III opioid partial agonist buprenorphine **formulations** for opioid use disorder

BUPRENORPHINE

○ Reduced deaths from overdose

○ France, 1995–2004: 79% reduction

○ Baltimore, 2002–2009: 61% reduction

From 225 → 87

Resurgence of overdose deaths in recent years with shift from pain pills to heroin and adulteration with fentanyl

IMPACT OF BUPRENORPHINE

- **DATA 2000:** law “carved a window” in Controlled Substances Act

- Extended political process

- Buprenorphine is the **only** medication approved

BUPRENORPHINE REGULATIONS

- Prescriber must obtain “waiver”
 - 8 hour training, in person or online
 - Given a second DEA number starting with “X”

BUPRENORPHINE REGULATIONS

- Rare overdose
 - Ceiling effect on respiratory depression
- Blocks other opioids at lower dose
 - High affinity for receptor site
- Less sedation

BUPRENORPHINE Vs. METHADONE

- **Less** euphoria for most patients
 - Partial agonist
- Legal to prescribe in **office based** practice
 - For waivered physicians
- **Pregnant opioid addicts:** less severe neonatal abstinence syndrome

BUPRENORPHINE Vs. METHADONE

○ Sublingual. mono vs. combo (with naloxone)

- Combo preferred to reduce diversion
- Greater incidence of nausea in combo

Possibly related to GI absorption of naloxone

Tip: spit out saliva after sublingual med dissolves

BUPRENORPHINE FORMULATIONS

○ Extended release

○ Implanted (**Probuphine**)

Requires surgical procedure
Limited use

○ Subcutaneous (**Sublocade**)

Recently released, limited experience

BUPRENORPHINE FORMULATIONS

- Mild withdrawal symptoms must be present to **avoid precipitated withdrawal**
 - **Transition from methadone**: reduce to 30 mg/day and wait 48 to 72 hours
 - **Recent problems** with heroin + “fentalogues”

Tramadol: up to 400 mg/day for 24 to 48 hours.

BUPRENORPHINE PROTOCOL

- 4 mg hourly until symptoms remit
 - Daily range- 8 to 24 mg
 - Lower initial dose (2 mg) when no recent use
- Can taper over 1 to 4 weeks but longer-term stabilization for months is preferable
 - High rate of relapse if use is short-term

BUPRENORPHINE PROTOCOL

- Eliminates withdrawal symptoms **quickly**
- Eliminates cravings
- Leaves them feeling “normal”

BUPRENORPHINE RESULTS

○ Improved treatment results

○ Longer stays in treatment

○ Fewer relapses

○ Fewer overdoses

BUPRENORPHINE RESULTS

○ Patients

○ Concern about getting off

○ Patient families

○ Negative publicity

ADDRESSING RESISTANCE

- Addiction treatment community

- "Not really clean"

- Narcotics Anonymous: "Unable to work the 12 steps"

ADDRESSING RESISTANCE

- Buprenorphine the **ideal** medication for this co-occurring condition
- Legitimate pain syndrome **does not require** DEA "X waiver" for prescriber

ADDICTED PAIN PATIENT

- Must **divide** into 3 to 4 doses/day
 - Analgesic effect is shorter
- May require **up to 32 mg/day**
 - Ceiling effect for analgesia is higher
 - Insurance may not cover

ADDICTED PAIN PATIENT

- Recommendation is to **maintain patient on agonist** and treat neonatal abstinence syndrome (NAS) with morphine
 - NAS severity reduced by rooming in

PREGNANCY AND OPIOID USE DISORDERS

- Methadone is still the **standard of care** but NAS can be severe
- Buprenorphine (mono): **less severe** NAS
 - Lower doses of morphine
 - Fewer days in NICU

PREGNANCY AND OPIOID USE DISORDERS

- Buprenorphine triggers **precipitated withdrawal** even when moderate withdrawal symptoms are present after 24 hours of abstinence

PROBLEM: FENTANYL ADULTERATED HEROIN

○ Solution: “tramadol bridge”

○ Opioid agonist with lower receptor affinity than buprenorphine

○ Initially not scheduled, now Schedule IV

○ Dosing 50 mg/hour up to 400 mg/day

150 to 200 mg most usual

○ Discontinue tramadol **12 hours** before starting buprenorphine

PROBLEM: FENTANYL ADULTERATED HEROIN

We agree with your analysis that tramadol may be administered (but not prescribed) to a patient for the purpose of relieving acute withdrawal symptoms **while arrangements are being made** for referral for treatment (with Kolmac or another provider), assuming that the administration occurs under the following conditions:

no more than one day's medication may be administered to the person or for the person's use at one time;
such emergency treatment may be carried out for **no more than 72 hours**; and
the **72-hour period cannot be renewed or extended**. (21 C.F.R. § 1306.07(b)).

Based upon our understanding of the circumstances under which Kolmac physicians administer tramadol, we believe that the application of the 72-hour exception to registration in these circumstances is reasonable. We understand that Kolmac physicians: (1) **utilize tramadol in emergency situations** to relieve acute withdrawal symptoms, while making arrangements for placement in a maintenance/detoxification program; (2) administer **no more than one day's medication** to the person or for the person's use at one time; and (3) utilize this treatment for **not more than 72 hours**.

TRAMADOL: 72 HR CSA EXCEPTION

- Over one million patients now taking it
 - Compared to a quarter million on methadone
- Incorporation into traditional 12-Step based residential treatment program
 - Hazelden/ Betty Ford project

EXPANDED USE OF BUPRENORPHINE

- Increased patient limit to 275 for physicians who...
 - Have addiction certification
 - Have had waiver for the 100 patient limit for one year
 - Or practice in a qualified health setting (provide counseling and accept insurance)
- New: NPs and PAs allowed to prescribe

EXPANDED USE OF BUPRENORPHINE

- Street use for relief of withdrawal rather than euphoria
- Street price has fallen below price of heroin

DIVERSION OF BUPRENORPHINE

- Prior authorization **now banned** in Maryland
- **Stabilization doses**
 - Vary by individual tolerance and preference
 - 12 mg as “blocking dose”

ONGOING ISSUES WITH BUPRENORPHINE

○ Co-morbid pain management

- Chronic

- Elective surgical procedures

ONGOING ISSUES WITH BUPRENORPHINE

○ Discontinuing

○ **When:** task versus time based

○ **How:** protocols

○ Relationship to long term recovery

ONGOING ISSUES WITH BUPRENORPHINE

○ “Safety sensitive” workers

- Opioid addicted physicians in many states are **not allowed to** regain license to practice if taking buprenorphine

Disagreements about mild cognitive impairment

BUPRENORPHINE CONTROVERSIES

- Traditional residential rehabilitation programs
 - Most “Minnesota Model” programs do not offer buprenorphine to patients beyond detoxification

BUPRENORPHINE CONTROVERSIES

○ Narcotics Anonymous

- Some groups **restrict participation** of members on buprenorphine: welcome but not equal
- Patients feel **“caught in the middle”** and tend either to discontinue buprenorphine earlier or avoid NA

BUPRENORPHINE CONTROVERSIES

- **How long** should a person stay on it?
- What about studies that suggest no benefit from increased therapy?
 - Role of therapy versus medication

BUPRENORPHINE: UNANSWERED QUESTIONS

○ Full agonist: methadone

○ **Pro:** stabilizes opioid system, reduces pain

○ **Con:** access is limited, can be abused, overdoses, discontinuation

SUMMARY

○ **Partial Agonist:** buprenorphine (Suboxone, Subutex)

○ **Pro:** stabilizes opioid system, reduces pain

○ **Con:** discontinuation

SUMMARY

○ **Antagonist:** naltrexone (Revia), Vivitrol

○ **Pro:** no abuse, easy to discontinue

○ **Con:** no opioid system stabilization or pain reduction

SUMMARY



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HEALTH SYSTEM

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Leaders in addiction treatment since 1973